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Acute Viral Hepatitis Types E, A, and B Singly and in Combination in Acute Liver Failure in Children in North India

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The aetiological agents responsible for, and the outcome of, acute liver failure were investigated prospectively in 44 children (29 males, 15 females) attending a tertiary health care facility in India. The children were between the ages of 2 months and 13 years. Studies for viral infections and other etiologies could be carried out in 40 patients. Specific aetiological labels were possible in 35 (87.5%) patients. Thirty (75%) had evidence of acute viral hepatitis. Acute hepatitis E virus (HEV) infection was found in a total of 18 children, with hepatitis A (HAV) in 16, hepatitis B in 5, and C in 1. Seven had isolated infection with hepatitis E, five with A, and four with B. Nine had both E and A infection.

Superinfection of HEV was observed in a child with Indian childhood cirrhosis (ICC). Acute HEV infection was confirmed by immunoblot assay in all the patients and in eight of these, HEV-RNA was also detected in the serum. HAV was involved in 37.5% of cases with isolated infection in 10% (4 of 40). The aetiological factors associated with acute liver failure, apart from HAV and HEV, were other hepatotropic viruses (22.5%), Wilson's disease (5%), ICC (5%), and hepatotoxic drugs (7.5%). In five patients, no serological evidence of acute viral hepatitis could be found, neither did the metabolic screen yield any result. It was observed that enterically transmitted hepatitis viruses (HAV and HEV) were associated with 60% of acute hepatic failure in children. Mixed infection of HAV and HEV formed the single largest aetiological subgroup. In developing countries, where hepatitis A and E infections are endemic, severe complications can arise in the case of mixed infection. This may contribute to most of the mortality from acute liver failure during childhood.

KEY WORDS: acute liver failure, children, fulminant hepatic failure, subacute hepatic failure, hepatitis A virus, hepatitis E virus

INTRODUCTION

Acute viral hepatitis is an endemic public health problem in India and other developing countries, which generally have poor sanitary and hygienic standards [Annonymous, 1990]. The infections frequently assume epidemic proportions with further increase in the morbidity and mortality [Krawcznski, 1993]. Liver failure is a rare but potentially fatal complication of acute hepatitis, and is characterised by rapid and progressive deterioration of liver function from massive/bridging hepatocellular necrosis leading to encephalopathy.

Liver failure due to non-A, non-B hepatitis (NANBH) was suspected in 4–60% of cases in various published paediatric [Psacharopoulos et al., 1980; Zacarias et al., 1987; Chang et al., 1987; Bhaduri et al., 1992] and adult [Bernuau et al., 1986; Tandon et al., 1986; Williams and Wendon, 1990] case series. NANBH infections were formerly a diagnosis of exclusion based on the absence of immunological markers of infection for the hepatitis A and B viruses (HAV, HBV). The advent of immunological tests for and the recent cloning of the hepatitis C virus (HCV) and hepatitis E virus (HEV) genome have led to the evaluation of these viruses as aetiological agents of the presumed NANB viral fulminant hepatic failure (FHF). HCV is primarily responsible for post-transfusion hepatitis and spreads by the parenteral route. The role of HCV in FHF is not clear. Although FHF due to HCV has been diagnosed in Japan [Muto et al., 1990], others have failed to demonstrate evidence of HCV in FHF patients in the United States [Liang et al., 1993] and Europe [Feray et al., 1993]. HEV has been identified as a major aetiological agent for enteric NANBH in several Asian and African countries [Krawcznski, 1993; Annonymous, 1994]. It usually runs an acute course normally resulting in resolution but also causes significant mortality, primarily because of FHF in pregnant women [Annonymous,

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1994]. In a recent study of adult patients from India, HEV was detected in 62% of the sporadic fulminant NANBH cases [Nanda et al., 1994]. Potential contribution of HEV hepatitis in the endemic areas to the aetiology of childhood liver failure is not known. The additional significance of HEV infection in childhood is the common enteral route of HAV and HEV infection and susceptibility of the children to these hepatotropic viruses, particularly in the developing societies where standards of hygiene and sewage disposal are not of the desired standard.

The present study was carried out to investigate the viral aetiology in paediatric patients with acute liver failure.

MATERIALS AND METHODS

Subjects

Forty-four children younger than 14 years of age, who were admitted with acute liver failure to the intensive care unit of the Department of Paediatrics at the All India Institute of Medical Sciences, New Delhi, India between January 1993 and December 1994, were investigated.

Acute liver failure includes FHF and subacute hepatic failure (SAHF) as defined below [Acharya et al., 1993]. FHF was defined as the occurrence of hepatic encephalopathy within 4 weeks of onset of jaundice, in the absence of pre-existing symptoms suggestive of liver disease. Patients were labelled as SAHF if the encephalopathy occurred between 4–24 weeks after the onset of jaundice.

Study Design

This was a case series of children with acute liver failure collected prospectively from a tertiary care health facility for the investigation of the aetiology and outcome.

Patients

Details of the clinical symptoms and findings were recorded in a structured questionnaire. Investigations were done to establish liver dysfunction, viral aetiology of hepatitis, and histological findings whenever consent to obtain post-mortem biopsy was available. Serum, urinary copper, and ceruloplasmin levels were estimated if the viral markers were negative or if strong clinical suspicion of Wilson's disease was present.

Liver function tests included serum total and direct bilirubin, alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), serum alkaline phosphatase (SAP), proteins, prothrombin time, sugar, urea, and ammonia levels. Post-mortem liver biopsies of 23 patients were available and confirmed the diagnosis.

Hepatitis Virological Screening

Serum was separated from 5 ml venous blood and stored aseptically in aliquots of 100 μl at − 70°C before processing for serological diagnosis. Patients were screened for IgM anti-HAV, HBsAg, IgM anti-HBcAg, and IgM anti-HDV using commercial micro-ELISA kits (Organon Teknika, Boxtel, The Netherlands). Second-generation ELISA (Abbott Laboratories, North Chicago, IL) was used to detect antibody to HCV antigens. All assays were carried out as per the manufacturers' guidelines.

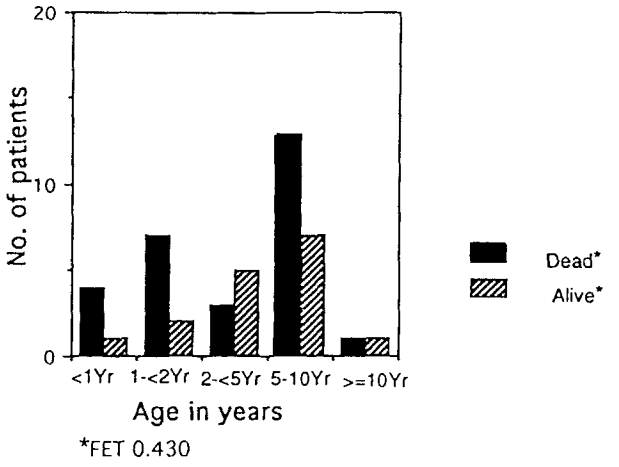

Fig. 1. Outcome in relation to age at presentation.

For the detection of IgM anti-HEV, an immunoreactive HEV peptide (comprising amino acids 91–123 of open reading frame [ORF] 3) was used as described earlier. The usual positive samples gave an OD value above 1.0, and the negative value was below 0.3 [Nanda et al., 1995].

HEV-RNA Assay

Detection of HEV-RNA in sera by reverse transcription-polymerase chain reaction (RT-PCR) was carried out as described earlier [Nanda et al., 1994].

Immunoblot Analysis

The purified recombinant ORF 3 antigen was separated on a 12% polyacrylamide gel with sodium dodecyl sulphate (SDS) and blotted onto nitrocellulose membranes (Schleicher & Schuell, GmBH) using standard procedures [Panda et al., 1995]. The assay was further confirmed using a peptide competition. Briefly, the ORF 3 peptide encompassing amino acids 91–123 was included in the primary incubation mix (1 μg peptide per 100 μL of bicarbonate buffer, pH 9) along with an appropriate dilution of serum, the other steps remaining unchanged from the standard protocol.

RESULTS

Forty-four children (29 males, 15 females) with acute liver failure between the ages of 2 months and 13 years were investigated during the study period. There were 5 children younger than 12 months; 9 between 1 and 2 years; 8 between 2 and 5 years; and 22 over 5 years of age (Fig. 1). Thirty-three children (75%) had FHF and SAHF was present in 11 (25%) who had onset of enceph-

TABLE I. Acute Liver Failure in Children, Etiology, and Outcome

Aetiological factors	FHF (n = 33)	SAHF (n = 11)	Dead	Total (n = 44)
HAV	4	0	0	4
HBV	3	1	3	4
HEV	2	4	4	6
HAV + HEV	8	1	3	9
HBV + HEV	1	0	0	1
HBV + HCV + HEV	1	0	1	1
HAV + HBsAg+ve	1	0	1	1
HBsAg+ve alone	2	0	1	2
ICC + HAV	0	1	1	1
ICC + HEV	1	0	1	1
Wilson's disease	0	2	2	2
Drug induced	3	0	3	3
Viral marker -ve	5	0	4	5
Sample lost	2	2	4	4

alopathy 29–145 days after jaundice was noticed by the main care provider.

Post-mortem biopsies from all 23 patients had the pathological features consistent with acute massive hepatocellular necrosis. In addition, two patients showed histological features suggestive of Indian childhood cirrhosis [ICC]; [Bhave et al., 1982]. Two patients of Wilson's disease had extensive copper deposits in the liver parenchyma.

Etiology

Studies for viral and other aetiologies were carried out in 40 patients (Table I). Samples were misplaced in four remaining patients. Specific aetiological labels could be given to 35 of 40 patients (87.5%).

The laboratory criteria used for specific diagnosis of viral infections were as follows: HAV, positive for IgM anti-HAV; HBV, positive for IgM anti-HBc; HCV, positive for anti-HCV antibody and HCV-RNA in patients' serum by RT-PCR; HEV, positive for IgM anti-HEV, Western blot positive for ORF-3, and/or positive for viral RNA in serum.

Evidence of one or more hepatitis viral infections was present in 75% (30 of 40) of the patients. Mixed infection with HAV and HEV constituted the single largest group (9 of 40; 22.5%) of acute liver failure patients. Acute hepatitis E infection (IgM anti-HEV) was present in 45% (18 of 40) of children either as an isolated infection (15%), as a mixed infection with other viruses (27.5%), or as a superimposed infection in a child with ICC (2.5%). Acute HEV infection was confirmed by immunoblot assay in all patients. In 8 of these 13 patients, serum HEV-RNA was also detected. HAV was involved in 37.5% of patients with isolated infection in 10% (4 of 40) of patients. Thus, water or food-borne hepatitis infection was present in 24 of 40 patients (60%) in whom the aetiology could be established.

There were two patients with Wilson's disease and another two had ICC. All four patients were completely asymptomatic before the onset of the present illness; ICC patients had super-added HAV or HEV infection but children with Wilson's disease did not have serological evidence of acute viral hepatitis. In five patients, no serological evidence of acute viral hepatitis could be found, neither did the metabolic screen yield any result. Nevertheless, all of them had acute hepatitis-like onset with fever, vomiting, anorexia, and upper-respiratory tract infection (URI)-like symptoms before appearance of jaundice and later on encephalopathy.

Two children were receiving anti-tubercular drugs (INH, rifampicin, pyrazinamide, and ethambutol) for 2 and 4 weeks, respectively, before they developed acute liver failure. Another patient had acute lymphatic leukaemia and was receiving methotraxate, vincristine, L-asparaginase, and donorubicin for 10 days before developing hepatic encephalopathy. These three patients had no evidence of acute hepatitis viral infection.

Although the number of SAHF patients was small, the aetiology of two types of liver failures was similar (Table I).

Clinical Profile

Patients presenting with liver failure within 4 weeks (FHF) and between 4–24 weeks (SAHF) after noticing jaundice by the main care provider were compared for clinical features.

Age and sex distribution, clinical symptoms of nausea, vomiting, abdominal distension, oedema, bleeding tendency, melaena, haematemosis, history of contact with a jaundiced person within or outside the family, and blood transfusions were similar for FHF and SAHF patients. Ascites was present in 18 (54.6%) children with FHF as compared to 9 (81.8%) SAHF patients ($P = 0.16$).

There were significant differences in the biochemical profile of the patients in the two categories (Table II). The total bilirubin was less statistically significant in FHF patients as compared to patients with SAHF ($P = 0.04$; Wilcoxon rank sum test [WRST]).

Outcome

The outcome of patients suffering from both fulminant as well as subacute liver failure was poor. The mortality was 63.6% (28 of 44), irrespective of the type of liver failure; 20 of 33 FHF patients (60.6%) and 8 of 11 SAHF patients (72.7%) died ($P = 0.72$). Age-related mortality is described in Figure 1. The relationship between aetiology and outcome is shown in Table I. The outcome in relation to the grade of encephalopathy at admission is described in Figure 2. There is a definite association between the grade of encephalopathy and mortality ($P < 0.001$). The two additional clinical features which had a major bearing on the outcome were coagulopathy and infection. Significant alteration in coagulopathy was considered when the prothrombin time was greater than 40 seconds. Seventy-five percent of the patients in this category expired (Table III). The evidence for infection were positive blood culture and/or presence of chest infection as demonstrated by chest x-ray. The mortality in patients with evidence of infection was 85% in comparison to a mortality rate

TABLE II. Biochemical Profile of Acute Liver Failure in Children

Biochemical parmeters	FHF (n = 33)	SAHF (n = 11)	Statistical test
Total bilirubin (μmol/L) median	128	376	WRST
(95% binomial exact CI)	(108–243)	(174–489)	$P = 0.038$
AST (IU/L) median	987	229	WRST
(95% binomial exact CI)	(391–1970)	(124–708)	$P = 0.09$
ALT (IU/L) median	1088	159	WRST
(95% binomial exact CI)	(325–2415)	(86–461)	$P = 0.048$
SAP (IU/L) median	548	272	WRST
(95% binomial exact CI)	(304–797)	(157–431)	$P = 0.06$
Total proteins (g/dl) (mean ± SD)	6.2 ± 1.8	6.7 ± 1.3	t test = 0.85 (df 42) $P = 0.40$
Albumin (g/dl) (mean ± SD)	2.9 ± 0.7	2.9 ± 1.3	t test = 0.33 (df 38) $P = 0.74$

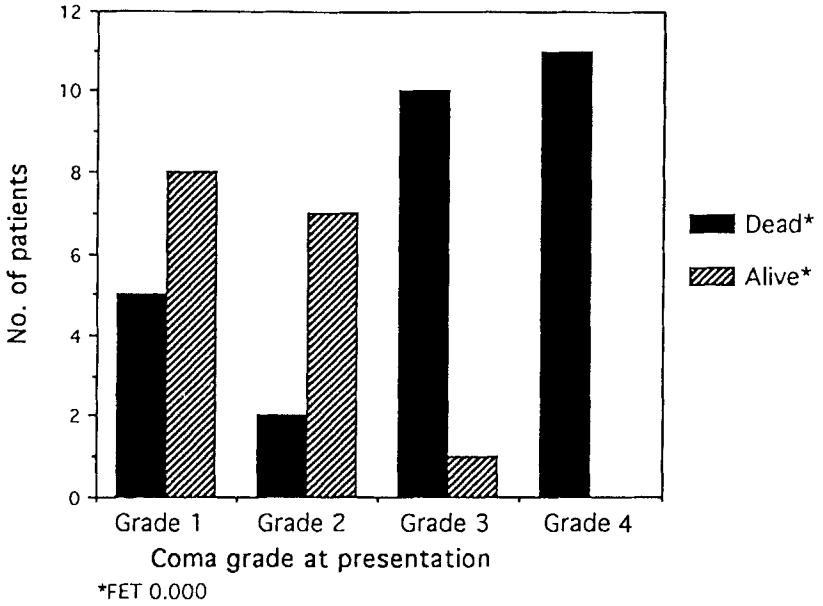

Fig. 2. Grade of hepatic encephalopathy at presentation and outcome.

of 25% in those having no infection (Table III). This difference was statistically significant ($P < 0.001$). The intracranial pressure measurement was not monitored routinely in this hospital.

DISCUSSION

The aetiological factors could be identified in almost 90% of patients with liver failure in the present study and 75% of the acute hepatic failure cases had evidence of infection with one or more hepatitis viruses. Mixed infection with more than one hepatitis virus formed the single largest aetiological subgroup accounting for 30% cases of acute liver failure.

The aetiology of acute hepatitis and its complication varies with the geographical region depending on the prevalent hepatitis virus types. Countries like Chile [Zacarias et al., 1987], South Africa [Friedland et al., 1991], and Turkey [Ozsoylu and Kocak, 1989] with a high HAV infection rate in childhood have reported it as the most frequent cause of acute liver failure. In contrast, Taiwan [Chang et al., 1987] being hyperendemic for the HBsAg carrier state, most of the FHF were HBV related. Reports from Europe indicate that although HAV did contribute to FHF, NANB viruses and drug toxicity were more important factors [Bhaduri et al., 1992]. HEV has only recently been identified and characterised. There has been conflicting evidence regarding HEV as a cause of hepatitis in children. Initial reports of enteric NANBH epidemics suggested that symptomatic HEV infection was infrequent in childhood [Naik et al., 1992], but subsequently several reports of sporadic hepatitis due to HEV in childhood have appeared. IgM anti-HEV antibodies were detected in 12–90% of the sporadic hepatitis cases among children (2 months to 15 years) in the Sudan [Hyams et al., 1992], Egypt [El-Zimaity et al., 1993; Goldsmith et al., 1992], and Somalia [Mushahwar et al., 1993]. In a recent hepatitis epidemic in North India, serological evi-

TABLE III. Acute Liver Failure in Children: Outcome in Relation to Coagulopathy and Evidence of Infection at Presentation

Sl. no.	Parameters	Dead	Alive	Statistical test
1	Coagulopathy	21	1	FET[a]
	Prothrombin time >40 sec			0.000
2	Infection			
	a) +ve chest X-ray	18	3	FET[a]
	b) +ve blood culture	6	1	0.000
	Total	24	4	

[a]Fischer's exact test.

dence of HEV infection was present in 7.5% of the exposed children younger than 15 years and 20% of adults; none of the children had clinical illness, but 1.3% of the adult population did [Dilawari et al., 1994].

In the present study, HEV or HAV infection alone was present in 15% and 10% cases of FHF, respectively; in contrast mixed HAV and HEV infection was associated with 22.5% cases of acute liver failure. Faecoorally transmitted diseases are responsible for a large fraction of childhood mortality and morbidity in India and other poor countries with inadequate sanitary and hygiene conditions. Both HAV and HEV are spread through the faecal-oral route. Therefore, it was not surprising to have these two viruses, either alone or as a mixed infection, associated with most cases of acute liver failure in our study population. In the study among Egyptian children [Hyams et al., 1992], only 2 of 41 children with acute hepatitis A and E had mixed HAV and HEV infection. In our own series of 52 acute hepatitis patients, one child had mixed HAV and HEV infection; this child had total bilirubin levels of 393 μmol/L (unpublished observations). Thus, inferring from the low prevalence of HEV-related clinical illness and FHF during epidemics and HAV infection being a mild disease in childhood, it appeared that a mixed infection of HAV and HEV increased the risk of acute liver failure in children. It is, however, not possible to say whether such mixed infections are sequential or occur simultaneously. This may influence the severity of hepatitis illness.

In the study by Feray et al. [1993] of fulminant hepatitis B, HCV-RNA was present in 8 of 17 of the patients. Chang et al. [1993] reported the presence of HCV antibodies in one of six children with NANB fulminant hepatitis but in none of the seven children with HBV-related FHF. In our study, HBV was associated with acute liver failure in 22.5% of patients, about half of which were isolated infection; three patients had only HBsAg circulating; and in another 5%, mixed infections were present (none had delta infection). A single patient had IgG antibodies to HCV along with circulating HCV-RNA, but had concomitant evidence of acute HBV and HEV infection. There was no history of blood transfusion in this patient in the previous 12 months. It was therefore difficult to assign causal role to any single agent. In another study of NANB fulminant hepatitis by Nanda et al. [1994], 22% of patients had both HCV and HEV-RNA. These studies stress that HCV may have only a minimal role in sporadic FHF without defined aetiology but may be contributing to severe forms as coinfection or superinfection with another hepatotropic virus. There was an additional patient with serological evidence of acute HBV and HEV infection. Although HEV superinfection has been noticed in HBsAg carriers [Jameel et al., 1992], it is not clear how acute HBV and HEV infection could occur together, when the route and course of infection of the two viruses are broadly different. A previous study, also from Delhi [Panda et al., 1989], reported mixed HAV and HBV infection in children with acute hepatitis. These cases may be examples of false positivity or situations where one infection (HEV) activated a previously latent or subclinical infection (HBV). Persistent HEV viraemia has been reported in a few patients [Nanda et al., 1995], and thus mixed HBV and HEV infection may be transmitted through nonenteral routes. However, the issue needs further study.

ICC is a chronic liver disease unique to the Indian subcontinent [Bhave et al., 1982]. In the present series two children (age 1 year and 2 years), without any previous history of symptoms suggestive of liver disease, presented for the first time with hepatic encephalopathy and had IgM antibodies to HAV or HEV. HEV-RNA was also present in the patient along with IgM anti-HEV antibodies. Post-mortem biopsies in both patients showed characteristic histological features of ICC along with coarse granular deposits of copper-associated protein and normal ceruloplasmin levels [Bhave et al., 1982]. The acute viral insult superimposed to the underlying ICC may have precipitated FHF which has been reported in up to 12% of ICC patients. It is conceivable that viral infections, particularly those producing hepatitis, may be responsible, at least in some cases, for acute decompensation of ICC patients or other metabolic disorders like Wilson's disease [Sallie et al., 1994]. In the present series, there were two patients with FHF who had increased urinary and serum copper excretion along with increased liver copper deposits, but hepatitis viral markers were absent. These patients were labelled as having Wilson's disease.

Anti-tubercular drugs have been associated with drug-induced FHF in both adults and children [Tsagar et al., 1985; Tuberculosis Research Centre, 1986]. Two patients labelled as having anti-tubercular drug-induced FHF in the present series had no evidence of any acute hepatitis infection. Paracetamol was reported to be an important cause of FHF in a case series from London [Bhaduri et al., 1992]. The difference could be due to differential patterns of hepatotoxic drug usage in various communities.

There were 12.5% patients who did not have a specific aetiological label, although the onset of infection was similar to that of acute viral hepatitis. This is unlike the data available from developed countries. Other studies of adults in India indicate that close to 20% of patients with acute hepatitis and acute liver failure do

not have evidence of infection with known hepatotropic viruses (Panda et al., unpublished observations).

SAHF is an ill-defined entity [Tandon et al., 1988]. The pathophysiological events that differentiate it from FHF are poorly understood. Unlike chronic hepatitis, SAHF patients have a relentless and often a fatal outcome over several weeks or months [Acharya et al., 1993; Tandon et al., 1988]. In studies of adult subjects with hepatic failure, SAHF is reported less often in European [Bernuau et al., 1986; Gimson et al., 1986] series of acute liver failure as compared to Indian series [Nanda et al., 1994; Acharya et al., 1993; Tandon et al., 1988], wherein as high as 50% of all acute liver failures present later than 4–8 weeks after the onset of initial hepatitis symptoms. The contribution and clinical characteristics of SAHF in the paediatric age group is not known. SAHF was encountered in 27% (11 of 41) of acute liver failure patients described in this series. The number was too small to comment on the characteristic clinical features of the syndrome. However, generally the clinical features, biochemical profile, and mortality pattern conformed to those described for adult patients from the same centre [Tandon et al., 1988]. Similar to a recently published series of adult patients [Nanda et al., 1994], acute HEV infection was the predominant aetiological factor associated with paediatric patients with SAHF (Table I). The profile of SAHF and pathogenetic mechanisms needs to be described in a larger number of paediatric patients to understand the disease better.

In summary, enterically transmitted hepatitis viruses, HAV and HEV, were associated with 60% of the cases of acute hepatic failure. Mixed infection of HAV and HEV formed the single largest aetiological subgroup causing acute hepatic failure. In developing countries with endemic hepatitis A and E infections, severe complications associated with mixed infection may be contributing acutely to the high mortality rates associated with these viruses.

REFERENCES

Acharya SK, Dasarathy S, Tandon BN (1993): Should we redefine acute liver failure? Lancet 342:1421–1422.

Annonymous (1990): The A to F of viral hepatitis (editorial). Lancet 336:1158–1159.

Annonymous (1994): Hepatitis E: From hypothesis to reality (editorial). Indian Journal of Gastroenterology 13:39–43.

Bernuau J, Rueff B, Bentamou J (1986): Fulminant and sub-fulminant liver failure: Definitions and causes. Seminars in Liver Disease 6:97–106.

Bhaduri B, Lau JYN, Heaton N (1992): Acute hepatic failure in childhood: Etiology, prognostic indicators and role of orthotopic liver transplant. Journal of Paediatric Gastroenterology and Nutrition 15:342 (Abstract).

Bhave SA, Pandit AN, Pradhan AM, Sidhyae DG, Kantarjian A, Williams A, Talbot IC, Tanner MS (1982): Liver disease in India. Archives of Diseases of Childhood 57:922–927.

Chang MH, Lee CY, Chen DS, Hsu HC, Lai MY (1987): Fulminant hepatitis in Taiwan: The important role of hepatitis B virus. Journal of Paediatrics 111:34–39.

Chang MH, Lee CY, Chen DS (1993): Minimal role of hepatitis C virus infection in childhood liver disease in an area hyperendemic for hepatitis B infection. Journal of Medical Virology 40:322–325.

Dilawari JB, Kartar Singh, Chawla YK, Ramesh GN, Chauhan A, Bhusnurmath SR, Sharma TR, Sokhey CS (1994): Hepatitis E virus: Epidemiological, clinical and serological studies of a north Indian epidemic. Indian Journal of Gastroenterology 13:44–48.

El-Zimaity DMT, Hyams KC, Imam IZE, Watts DM, Bassily S, Naffea EK, Sultan Y, Emara K, Burans J, Purdy MA, Bradley DW, Carl M (1993): Acute sporadic hepatitis E in an Egyptian paediatric population. American Journal of Tropical Medicine and Hygiene 48:372–376.

Feray C, Gigou M, Samuel D, Reyes G, Bernuau J, Reynes M, Bismuth H, Brechot C (1993): Hepatitis C virus RNA and hepatitis B virus DNA in serum and liver of patients with fulminant hepatitis. Gastroenterology 104:549–555.

Friedland IR, Zuckerman M, Kala UK, Parbhoo KB (1991): Fulminant hepatitis in children: Report of 12 cases. Annals of Tropical Paediatrics 11:207–211.

Gimson AES, O'Grady J, Ede RJ, Portmann B, Williams R (1986): Late onset hepatic failure: Clinical, serological and histological features. Hepatology 6:288–294.

Goldsmith R, Yarbough PO, Reyes GR, Fry KE, Gabor KA, Kamel M, Zakaria S, Gaffar AY (1992): Enzyme linked immunosorbent assay for diagnosis of acute sporadic hepatitis E in Egyptian children. Lancet 339:328–331.

Hyams KC, Purdy MA, Kaur M, McCarthy MC, Hussain MA, el-Tigania A, Krawcznski K, Bradley DW, Carl M (1992): Acute sporadic hepatitis E in Sudanese children: Analysis based on a new Western blot assay. Journal of Infectious Diseases 165:1001–1005.

Jameel S, Durgapal H, Habibullah CM, Khuroo MS, Panda SK (1992): Enteric non-A non-B hepatitis: Epidemics, animal transmission, and hepatitis virus E detection by polymerase chain reaction. Journal of Medical Virology 37:263–270.

Krawcznski K (1993): Hepatitis E. Hepatology 17:932–941.

Liang TJ, Jeffers L, Reddy RK, Silva M, Cheinquer H, Feindeo A, Medina MD, Yarbough P, Reyes AR, Schiff ER (1993): Fulminant or subfulminant non-A non-B viral hepatitis. The role of hepatitis C and E viruses. Gastroenterology 104:556–562.

Mushahwar IK, Dawson GJ, Bile KM, Magnius LO (1993): Serological study of an enterically transmitted non-A, non-B hepatitis in Somalia. Journal of Medical Virology 40:218–221.

Muto Y, Sugihara J, Ohnishi H, Nishioka K (1990): Antihepatitis C virus antibody prevails in fulminant hepatic failure. Gastroenterologica Japonica 25:32–35.

Naik SR, Aggarwal R, Salunke PN, Mehrotra NN (1992): A large water borne viral hepatitis E epidemic in Kanpur, India. Bulletin of World Health Organisation 70:597–604.

Nanda SK, Yalcinkaya K, Panigrah AK, Acharya SK, Jameel S, Panda SK (1994): Etiologic role of hepatitis E virus in sporadic fulminant hepatitis. Journal of Medical Virology 42:133–137.

Nanda SK, Ansari IH, Acharya SK, Jameel S, Panda SK (1995): Protracted viremia during acute sporadic hepatitis E virus infection. Gastroenterology 108:225–230.

Ozsoylu S, Kocak N (1989): Acute hepatic failure related to hepatitis A. Lancet 313:901.

Panda SK, Datta R, Gupta A, Kamat RS, Madangopalan N, Bhan MK, Rath B, Guha DK, Nayak NC (1989): Etiologic spectrum of acute sporadic viral hepatitis in children in India. Tropical Gastroenterology 10:106–110.

Panda SK, Nanda SK, Zafrullah M, Ansari IH, Ozdener MH, Jameel S (1995): The Indian strain of HEV: Cloning, sequence and expression of the structural region and antibody responses in sera from an area of high HEV endemicity. Journal of Clinical Microbiology (in press).

Psacharopoulos HT, Mowat AP, Davies M, Silkdba P, Williams R (1980): Fulminant hepatic failure in childhood. Archives of Diseases of Childhood 55: 252–258.

Sallie R, Chiyende J, Tan KC, Bradley D, Portmann B, Williams R, Mowat AP, Vergani GM (1994): Fulminant hepatic failure resulting from coexistent Wilson's disease and hepatitis E. Gut 35:849–853.

Tandon BN, Joshy YK, Tandon M (1986): Acute liver failure: Experience with 145 patients. Journal of Clinical Gastroenterology 8:664–668.

Tandon BN, Joshi YK, Acharya SK (1988): Subacute hepatic failure. National Medical Journal of India 1:124–127.

Tsagar OS, Mataki-Emmanouilidon T, Karida-Kavaliotis S, Manios S (1985): Hepatotoxic reactions in children with severe tuberculosis treated with isoniazid-rifampin. Paediatric Infectious Diseases 4:270–273.

Tuberculosis Research Center, Madras and National Tuberculosis Institute, Banglore (1986): A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum positive pulmonary tuberculosis in South India. American Review of Respiratory Diseases 134:27–33.

Williams R, Wendon J (1990): Clinical syndrome and etiology of fulminant hepatic failure. In Williams R (ed): "Proceedings of the Eleventh BSG/SK&F International Workshop on Acute Liver Failure," Ferndown, UK, September 24-25, Belgium SKF, pp 1–5.

Zacarias J, Brinck P, Cordero J, Velasco M (1987): Etiologies of fulminant hepatitis in paediatric patients in Santiago, Chile. Paediatric Infectious Diseases J 6:686–687.